FOSTERING COMMUNICATION AND COLLABORATION

The NIH Catalyst

A PUBLICATION FOR NIH INTRAMURAL SCIENTISTS

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Roadmap Recap: A Year's Worth Of Milestones

by Fran Pollner

Praised for her "flawless execution of a very complex process" by NIH Director Elias Zerhouni, NIH Roadmap coordinator Dushanka Kleinman delivered a first-year Roadmap progress report at the December 2004 meeting of the Advisory Committee to the [NIH] Director.

In general, she said, 2004 could be characterized as a year of seeding new tools and technologies for the team science and clinical research of the future. Among the year's achievements:

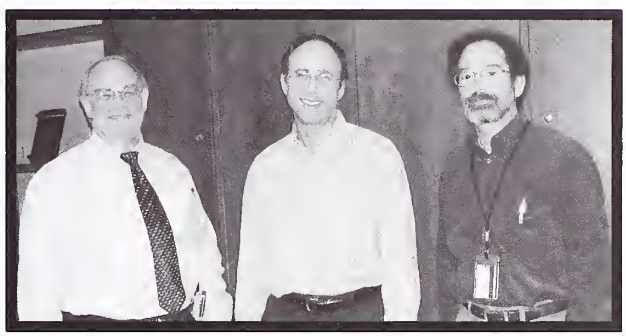
- Establishing four National Centers for Biomedical Computing (with more to be funded in 2005)
- Launching the Patient-Reported Outcomes Measurement Information System, with seven grants, six to primary research centers
- Funding 20 nanomedicine concept-planning grants, which will form the solicitation base for Nanomedicine Development Centers in 2005 and 2006 (see story, page 1)
- Funding 21 interdisciplinary research exploratory centers and identifying institutional barriers to interdisciplinary research
- Conducting an inventory of clinical research networks (500 already identified) to identify best practices
- Launching 12 pilot studies to assess the feasibility of integrating and increasing the interoperability of clinical research networks and to pave the way for NECTAR (National Electronics Clinical Trials and Research network)
- Designing the scope for planning grants to be funded in 2005 and 2006 for regional translational research centers, as well as for core services similar to the NCI RAID program (see story, page 7)
- Completing the first round of the NIH Director's Pioneer Award (see **<http://nihroadmap.nih.gov/pioneer/>**), with more than 1,300 nominees vying for the nine awards ■

Nanomedicine Initiative: A New Pathway to Discovery With Evolving Turns and Destinations

by Karen Ross

The aim of nanomedicine, one of nine major NIH Roadmap initiatives, is to treat disease by intervening at a molecular level. It is a close cousin of nanotechnology, which is concerned with building devices that are 0.1 μ or less in size. (For reference, the head of a pin is 2,000 μ, a typical human cell is approximately 5 μ, and a large protein complex is approximately 0.005 μ.)

Nanomedicines, for example, could beof tiny machines that compensate for the function of defective proteins or very precisely targeted pharmaceuticals that have no side effects.



Karen Ross

Intrigued by the Invisible: *NEI Director Paul Sieving (left) and NHGRI tech development guru Jeffery Schloss (right), co-chairs of the NIH Roadmap Nanomedicine Implementation Group, flank Richard Fisher, director of the NEI Corneal Diseases Program and Nanomedicine Project team leader*

Deeper Levels of Quantitation

Before these treatments can become a reality, scientists first need a detailed, quantitative understanding of cellular processes. Many of today's approaches to biochemistry and molecular biology are much more descriptive than quantitative, says Jeffery Schloss, director of Technology Development Coordination, NHGRI, and one of the chairs of the implementation group that directs the Roadmap nanomedicine initiative.

The nanomedicine initiative, Schloss says, encourages scientists to take an engineer's view of the cell—to think of molecular pathways as circuits and to make careful measurements of physical and chemical processes that take place.

Nanotechnology will contribute both the tools to make these measurements and, ultimately, the devices that can remodel molecular circuits. Furthermore, Schloss observes, biological pathways are themselves excellent examples of robust systems that operate at the "nano" scale.

But he does sound a cautionary note. However exciting and promising the field of nanomedicine may be, it is also a field in its infancy.

It is extremely hard to predict what direction nanomedicine research will take in the near future, Schloss says, and this uncertainty has presented special challenges to the nanomedicine imple-

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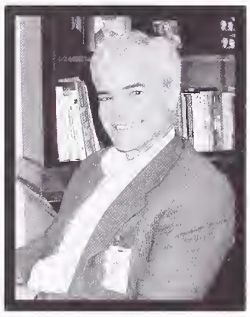
Intramural Research Accomplishments

This issue of *The NIH Catalyst* includes our annual enumeration of selected intramural scientific achievements.

At a time when budgets are tightening and scrutiny and restrictions are increasing, it is a heartening reminder of the quality and impact of our work. The special intramural environment that facilitates this science is what attracted most of us to the NIH and what keeps us here through thick and thin.



Michael Gottesman

In my talk at the NIH research festival this year, I focused on three components of the intramural program that have been especially critical in its success. Richard Florida, in his book *The Rise of the Creative Class,* referred to these as the three T's: Technology, Talent, and Tolerance (for out-of-the-box and creative endeavors as well as a diverse work-force). The abbreviated list of accomplishments beginning on page 8 highlights all three of these aspects of the intramural program.

NIH continues to be pre-eminent in the discovery and characterization of genes involved in disease, especially in cancer, mental illness, and neurological problems such as Parkinson's disease. Owing to the establishment of an NHGRI intramural program and genetics core facilities several years ago, we had a big headstart on disease-gene discovery, and this technology has spread to most of the intramural program, facilitating bench-to-bedside applications of basic genomic research. The new Clinical Research Center will undoubtedly facilitate these advances.

There is probably no better place in the world than NIH for both laboratory and applied research in immunology. The research highlights include several examples of contributions to basic immunology, such as cytokine research, as well as specific contributions to HIV pathogenesis and vaccine development, including progress in both HIV and SARS. In addition to the extraordinary concentration of talent at NIH in these areas, we have several energetic trans-NIH grassroots scientific interest groups under the umbrella of the Immunology Interest Group, as well as the Vaccine Research Center, that facilitate communication and collaboration in these research areas.

Creativity in the intramural program is frequently manifested as novel interdisciplinary studies, amply illustrated in the list of annual achievements, that break down barriers between Institute-specific research programs. Because we tolerate and encourage structural biologists in NIDDK to work on HIV-AIDS and Alzheimer's disease, or cardiac physiologists in NHLBI to develop imaging tools relevant to neurobiology, we are able to make novel and innovative contributions to biomedicine.

Obviously this brief synopsis of achievements cannot do justice to the extraordinary breadth of intramural science. I hope it will serve to remind our scientific staff of why NIH is a very special place.

—Michael Gottesman
Deputy Director for Intramural Research

Accountable Authorship: Comments from NIH Scientists Who Took the Research Ethics Computer Course

by Joan Schwartz
Assistant Director, OIR

Joan Schwartz

In July we launched the Research Ethics Computer Course (<**http://researchethics.od.nih.gov**>), and I notified all of you about it through a column *in The NIH Catalyst* (July-August 2004 issue). Since then, I have received approximately 300 comments, via the built-in e-mail address for responses, and am pleased to report that 99 percent of them have been highly complimentary.

Some of the comments have raised stimulating questions about specific topics and/or quiz questions or cases, and the NIH Committee on Scientific Conduct and Ethics has decided to address those. Future issues of the *Catalyst* will contain responses to issues raised about the cases involving human subjects. We will also write about specific authorship questions regarding one of the cases.

In this column, I would like to address more generic authorship issues raised by three of our intramural scientists. Rose Mage, NIAID, provided a PDF file with the new *PNAS* authorship criteria, and Germaine Buck Louis, NICHD, noted that the International Committee of Medical Journal Editors <**http://www.icmje.org/**> has issued new guidelines for the biomedical journals regarding determination of authorship.

One general theme is the need for accountability, because frequently these days authors make specialized contributions to a paper. All the journals are asking that authors describe their specific contributions to the publication, either by checking off appropriate responses from the journal's list or putting the information into a footnote.

Authors are asked to agree on authorship order based on these contributions. The *PNAS* guidelines state that the corresponding author should be the guarantor of the paper. The journals agree that "gathering funds for the project, paying salaries, providing a conducive environment, being the spokesperson, or providing published reagents or procedures are not activities that warrant authorship without a significant contribution to the scientific content of the paper" (*PNAS* **101**:10495, 2004). They believe that these criteria will protect against ghost or gratuitous authorship.

These new guidelines represent extensions of the rules for authorship provided in the course. It would be worthwhile to discuss these in one of your future lab meetings.

Paul Kovac, NIDDK, raised a different kind of publication issue of concern to him. In the course module on publication and authorship, page 3 states: "Even though each paper should contain sufficient information for the informed reader to assess its validity, the principal method of scientific verification is not review of submitted or published papers, but the ability of others to replicate the results. Therefore, each paper should contain all the information necessary for other scientists to repeat the work and/or the complete list of references used to conduct the specific experiment." Page 4 makes the following points:

- "Scientists should not rush to publish.
- "Timely publication of new and significant results is important for the progress of science. But . . .
- "Each publication should make a substantial contribution to its field.
- "Fragmentary publication of the results of a scientific investigation or multiple publications of the same or similar data are not appropriate; e.g., using a tactic termed salami slicing or producing lots of LPUs (Least Publishable Units)."

Kovac has written a commentary, published in *Chemistry & Biodiversity* (**1**:606, 2004), in which he notes that the quality of chemistry papers has been declining despite increasing sophistication of methods, reagents, and instrumentation.

One reason is that the "number of papers whose experimental results cannot be reproduced because of lack of data presented, as well as the number of compounds described for the first time that have not been properly characterized, is increasing at an alarming rate."

Kovac, like many of us, is convinced that "the progress of science is not directly proportional to the number of pages available in journals."

As stated so elegantly by René Dubos (and inscribed on the sculpture bridge in the Science Court of the Hatfield Clinical Research Center): "In science as in other human activities, the speed of progress is less important than its direction."

These comments all address the basic issue of responsible authorship—the need to take responsibility for what is published, to acknowledge properly all the people who contributed to the research and the level of their contributions, and to publish only complete studies with all the necessary details available to enable replication.

Perhaps the most important result of heeding all this advice would be that there might be fewer—but better—journals and articles for busy scientists to read! ■

New Fogarty Scholar, Immunology Giant, To Be at NIH One Year

Giorgio Trinchieri, the discoverer of IL-12 and murine plasmacytoid dendritic cells (DC), has been named an NIH Fogarty Scholar for one year starting November 15, 2004.

Giorgio Trinchieri

Currently the director of the Schering-Plough Laboratory for Immunological Research in Dardilly, France, Trinchieri will pursue research focusing on:

- The interface between natural resistance and adaptive immunity, especially mechanisms regulating DC subsets, natural killer cells, and T cells
- The role of cytokines and DC in regulating early innate response to infection and deviation of the adaptive response
- Means to harness innate resistance for antitumor therapeutic effect based on tumor antigen–specific and nonspecific mechanisms.

Trinchieri will work closely with NIAID and NCI investigators involved in related research and will be based primarily in the Laboratory of Parasitic Disease, NIAID, according to Robert Seder, chairman of the Cytokine Interest Group, who nominated him. ■

Nanomedicine Initiative
continued from page 1

mentation group.

Nanomedicine is one of the five initiatives under the major NIH Roadmap theme "New Pathways to Discovery." The initiative is directed by an implementation group whose members are drawn from all over NIH.

Along with Schloss, the 16-member nanomedicine implementation group is chaired by NEI Director Paul Sieving, whose institute is responsible for administrative oversight of the initiative.

The group's primary mission is to develop a program that will fund the establishment of Nanomedicine Development Centers.

This initiative, Schloss and Sieving observe, has relevance to disciplines throughout the entire NIH. The tools and concepts that will emerge will enhance basic biological understanding and should eventually result in medical interventions that touch the mission of every institute.

Karen Ross

Overseeing the initiative to quantify the unseeable:
(left to right) Paul Sieving, Richard Fisher, and Jeffery Schloss

Approaching a Visionary Center

No one is sure yet just what a Nanomedicine Development Center will look like. The investigators that make up a center could all be from the same institution, or there could be a core group at one institution that has collaborators in other places.

"They can also be virtual centers; there's really no requirement for bricks and mortar," says Richard Fisher, director of the Corneal Diseases Program, NEI, and Nanomedicine Project team leader.

The idea, he says, is to bring in top investigators from many disciplines to work on a common problem. "They can work together across oceans; what's important is their chemistry."

The requirements for a center have intentionally been sketched out only in rough outline:

- A center should bring together scientists from a wide range of disciplines including biology, engineering, chemistry, physics, and mathematics.
- The group of centers that is funded should form a collaborative network that shares both intellectual and physical resources.
- The research should focus on developing quantitative approaches that are applicable to a wide range of biological problems.

The details have all been left to the creativity of the scientists who apply for funding. Says Sieving, "We want . . . the groups that are funded by this [initiative] to have free intellectual space to develop the concept of nanomedical technology in a way that we hope will speed its emergence."

A Unique Process

This degree of freedom is possible because of the unique process the implementation group devised for funding the centers.

Typically, when NIH program staff identify an area in biomedical science that needs investigation, NIH issues a request for applications (RFA), and interested scientists submit an application. Then, two levels of peer review, the study section and the advisory council of the funding NIH institute, are invoked to assess the scientific merit of the proposed work.

For the Nanomedicine initiative, however, the implementation team designed a multistep process whereby extramural investigators work collaboratively with NIH staff to craft the content of the Centers RFA that will be issued in April 2005.

The initiative was launched at a public meeting May 4, 2004, at NIH; approximately 300 scientists from all over the country attended. After this meeting, investigators were invited to submit a five-page "white paper" of their vision of a nanomedicine development center.

The implementation group received 81 such white papers, from which the members, in consultation with a group of extramural scientists, chose 20 to receive planning grants.

Criteria for judging the white papers included the characteristics of the suggested model systems; the attention paid to quantitative measurements and engineering design principles; and the multidisciplinary nature of the team's approach. Overall, the group sought to ensure the inclusion of a broad range of biomedical areas (see sidebar, page 5).

In another departure from the traditional grant-application process, in which investigators carefully guard the confidentiality of their proposals, representatives from each of the 20 groups will present more detailed 15-page proposals to each other and to members of the implementation group at a meeting to be held in March 2005.

This meeting, Fisher observes, will "really stimulate the interactive nature of the process." The cross-talk and ideas generated during the meeting, together with the applicants' written proposals, will inform the implementation group's final RFA for the Nanomedicine Development Centers.

In 2005, only the 20 groups that participated in the planning stages will be

NANOMEDICINE SAMPLER: PLUMBING THE DEPTHS OF CELLULAR PROCESSES

by Karen Ross

The 20 groups awarded nanomedicine development cen-ter planning grants reflect diverse scientific interests and approaches:

■ A group at Brown University, Providence, R.I., led by Clyde Briant plans to study the interactions between human tissues and foreign materials on a molecular level, with the goal of developing more biocompatible medical implants and devices.

■ Wah Chiu's group at Baylor College, Houston, wants to examine how molecular chaperones help proteins to fold into their correct three-dimensional structures. This research could lead to the design of protein-folding machines that could be used to fight diseases, such as Alzheimer's, that are thought to be caused by the accumulation of misfolded proteins.

■ On a similar theme, Yuri Lyubchenko's team at the University of Nebraska Medical Center, Omaha, will explore what causes proteins to misfold and aggregate. They will develop tools to observe individual proteins as they aggregate and techniques to manipulate these proteins in the test tube.

■ James Baker's group at the University of Michigan, Ann Arbor, proposes to study the structure and function of membranes using nanoscience tools. This work could lead to better strategies for delivering drugs to cells as well as a deeper understanding of agents that disrupt membranes.

■ Gang Bao of the Georgia Institute of Technology, Atlanta, leads a group that studies the biological nanomachines responsible for RNA synthesis and DNA repair. They will develop imaging tools that can reveal the behavior of single molecules inside cells.

■ Richard Wood and his group at the University of Pittsburgh will focus on the large protein complex responsible for nucleotide excision repair.

■ James Crowe and his team at Vanderbilt University, Nashville, Tenn., want to gain a detailed understanding of the signaling pathways triggered when the immune system encounters an invading microorganism. Ultimately they hope to be able to manipulate the immune response in individual cells or in the body of an organism.

■ Douglas Eaton of Emory University, Atlanta, and his group plan to use scanning probe microscopy techniques, which can zero in on structures as small as a molecule interacting with the surface of a cell, to study how cells communicate with each other.

■ A team at the University of Pittsburgh led by Susan Gilbert will investigate the motor proteins involved in mitosis at the nanometer level with the goal of developing better strategies for controlling cell proliferation.

■ Kevin Gillis' group at the University of Missouri, Columbia, plans to study the protein and lipid machines that move material into and out of cells. These machines are implicated in many diseases, including cystic fibrosis and diabetes, and are prominent drug targets.

■ Chih-Ming Ho at the University of California, Los Angeles, and his colleagues will use tools to visualize and manipulate the cytoskeleton, whose dynamic rearrangements are critical for many cellular processes.

■ Samuel Stupp and his team at Northwestern University, Evanston, Ill., also plan to tackle the cytoskeleton on the nanoscale. The group will study the assembly of cytoskeletal structures and the involvement of the cytoskeleton in cell division and movement.

■ Ehud Isacoff's team at the University of California, Berkeley, will study the membrane receptors that detect conditions in the extracellular environment and the signaling pathways that relay this information to the nucleus.

■ A group led by Eric Jakobsson at the University of Illinois, Urbana-Champaign, will embark on detailed studies of biological ion-conduction systems and apply this knowledge to the design of nanoconducting devices.

■ Gary Johnson and his team at the University of North Carolina, Chapel Hill, focus on the stressome, a multiprotein complex that responds to cellular stress. They have developed probes that can detect the conformation of individual components of the complex.

■ A group at the University of Connecticut School of Medicine and Dentistry, Farmington, Ct., led by Leslie Loew will address cellular processes on "supramolecular scale." These experiments will take a broader view than studies of individual molecules but provide more detail than studies done on a cellular level.

■ Edward Pugh and his colleagues at the University of Pennsylvania, Philadelphia, will study supramolecular cellular compartments (SMCCs) such as photoreceptors and nerve growth cones. They want to understand how these compartments assemble and eventually hope to develop artificial substitutes that can be used to treat diseases, including retinal degeneration, that are caused by defective SMCCs.

■ A group led by David Needham at Duke University, Durham, N.C., plans to apply engineering principles to the study of four biological problems: drug delivery, measurement of forces inside cells, inflammation, and orthopedic bioengineering. The knowledge they glean will be used to design nanoscale machines.

■ A Columbia University (New York, Morningside campus) team led by Michael Sheetz will explore the connections between cellular processes and physical factors such as spatial organization and mechanical force. This work could lead to improved production of artificial tissues and therapies to enhance tissue repair.

■ Wendell Lim's group at the University of California, San Francisco, plans to build machines that can direct cell movement. ■

allowed to respond to the RFA and of those, three or four groups will receive five-year grants to establish their centers; the grants will total $6 million.

Beyond 2005

The implementation group anticipates another $6 million for a second round of Nanomedicine Development Center grants. Competition for this second round will be more traditional but "informed by everything we've done and learned this first round," Fisher says.

The team hopes that at the end of five years the first-round centers will have become productive, self-sustaining entities.

The centers are expected to have a cohesive set of investigators, to have a well-defined, workable topic of study, and to have made substantial progress in their research, says Sieving.

As for their financial future, it is possible that they will continue to be supported by the Roadmap, or they might be adopted by individual institutes at NIH. Alternatively, they could seek out funds from regular NIH grant programs or from private agencies.

"We're hoping to build something so exciting," says Schloss, "that NIH and other agencies . . . can't resist putting more money into it." ■

On the Road to Clinical and Translational Research Careers

by Dianne Needham

As part of their so-called "year off" from school to engage in concentrated research, more than 250 medical and dental students converged on the NIH campus for the second annual Clinical Investigator Student Trainee (CIST) Forum.

For three days in November 2004, the students were immersed in lectures, panels, and workshops to fortify their nascent interest in becoming clinician investigators. They were invited to attend because they are currently participating in clinical and translational research fellowships—often referred to as "year-off" programs and sponsored by NIH and other academic medical centers around the country. (For info on the NIH program, see <**http://www.training.nih.gov/student/Pre-IRTA/previewinterim.asp**>.)

The CIST Forum focuses on scientific advances and careers in clinical or translational research. Frederick Ognibene, director of the CC Office of Clinical Research Training and Medical Education, explains: "It's an attempt to further capture and maintain the interest in academic careers already demonstrated by these students who have committed to a year of research in addition to their formal medical education. Hopefully, this program demonstrates that such careers can be both scientifically and personally rewarding."

Ernie Branson

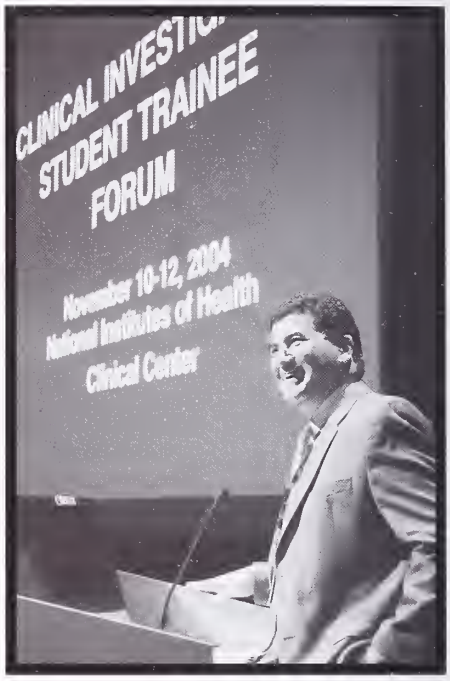
Enjoying the company: *NIH Clinical Research Training Program students (left to right) Julie Rosenthal, Samer Jaber, Arash Koochek, Robert Allison, Sinae Park, Chris Keh, and Rebecca Hommer visit with Frederick Ognibene (far right), director of the Office of Clinical Research Training and Medical Education, during a break in the CIST Forum program.*

Arpi Doshi and Arash Koochek, NIH Clinical Research Training Program students, don't need much convincing. Doshi, a student at the University of Michigan Medical School in Ann Arbor, has a strong interest in academic medicine. "Medical research is so important, yet we get bogged down in patient care. We need to step back," she observed, "and see what might make things better."

Koochek, a student at the University of Vermont College of Medicine in Burlington, already knows he will become what he calls a bridge scientist. "I am very patient-oriented but want to work with both patients *and* scientists. This will enhance my scientific-medical knowledge as well as my career," he said.

During the CIST Forum, established investigators representing both NIH and other academic medical centers presented their ideas and experiences in the realm of how to succeed as a physician-scientist; they also explored controversies in medicine and bioethics and translation from the bench to the bedside.

The CIST Forum is part of the thread in NIH's Roadmap tapestry within the initiative to re-engineer the clinical research enterprise—namely, to enhance and expand the scientific workforce.



Ernie Branson

From one seasoned clinical investigator to the next generation: *NIH Director Elias Zerhouni spoke to the CIST Forum student attendees about their future careers in clinical research.*

"Clearly, a goal is to have these 250 bright and energetic students continue in academic careers as physician-scientists participating in clinical research," Ognibene said. "The sponsoring partners will track the subsequent careers of the participants in the CIST Forum as they move from medical school to residencies, subspecialty training, and beyond," he said. He noted that in bringing seasoned and emerging physician-scientists together, the forum encourages and provides a base for continuing collaboration and networking.

Yale University School of Medicine (New Haven, Ct.) student and Doris Duke clinical research fellow Katherine Gergen-Barrett summed up her appreciation of the CIST Forum: "It is all about empowerment." ■

For More Information . . .

CIST Forum partners include NIH, the Howard Hughes Medical Institute, the Doris Duke Charitable Foundation, and the Sarnoff Endowment for Cardiovascular Science.

For more information on clinical research training opportunities at NIH, contact the Clinical Center's Office of Clinical Research Training and Medical Eduation at 301-496-9425 or visit online at

<**http://intranet.cc.nih.gov/clinicalresearchtraining**>.

For information on the NIH Roadmap initiative on "Re-engineering the Clinical Research Enterprise," see

<**http://nihroadmap.nih.gov/clinicalresearch/index.asp**>.

Re-engineering the Clinical Research Enterprise

A LOOK AT THE ROADMAP'S RAID FOR TRANSLATIONAL RESEARCH CORE SERVICES

by Annie Nguyen

February 2005 marks the beginning of an NIH Roadmap pilot program to expedite the transition of novel therapeutic discoveries to early-phase clinical trials.

A component of the Roadmap's clinical research re-engineering initiative, the NIH-RAID (rapid access to interventional development) pilot will make available, on a competitive basis, the means to address regulatory and/or technical barriers to moving a promising idea from the bench to bedside testing.

Process

According to Josephine Briggs, director of the Division of Kidney, Urologic and Hematologic Diseases, NIDDK, and co-chair of the implementation group for Translational Research Core Services, this pilot program will provide services for academic investigators, as well as for some intramural researchers, "of the sort that are more available in industry settings than in the academic world."

Such services include the technical resources to synthesize small molecules, peptides, and oligonucleotides for early-phase clinical studies; ADME testing (absorption, distribution, metabolism, and excretion) to monitor how a drug behaves in people; and the development of pharmacology assays on blood and urine samples.

The NIH-RAID pilot is modeled after the NCI Developmental Therapeutics Program and will rely on contractors who have established relationships with NCI—a resource "too valuable," Briggs commented, not to apply to this Roadmap initiative.

The new program will, however, have a separate review setting and administration, and the projects will not be limited to those related to cancer. It's anticipated that availability to the broader research community will accelerate discoveries for other major public health challenges.

Co-chaired by NCCAM Director Stephen Straus and including representatives from 13 different institutes, the implementation group will appoint a review board to select those projects to be awarded grants. Once the projects are actually approved, however, the oversight will largely go back to the co-sponsoring institute(s).

Annie Nguyen

Josephine Briggs

Funding to support individual projects will come from both the Roadmap and individual institutes, with the institutes assuming the bulk (three-fourths) of support in the specific disease areas akin to their mission. Briggs points out that institute co-sponsorship is critical to ensure disease-specific expertise in the oversight of the projects.

Applications for NIH-RAID awards will undergo a two-stage evaluation process (see chart below). The first stage will establish that the resources requested are within the scope of the pilot program and that there is institute co-sponsorship. Applicants selected from this pool will then be invited to submit a full proposal for assessment by an external panel of experts.

Projections

Asked what sort of projects NICHD might be interested in co-sponsoring, Phyllis Leppert, Reproductive Sciences Branch chief, cited research on the prevention of preterm labor and new leads in contraception as examples of areas that have not been adequately addressed by the private sector and would likely encounter translational barriers without NIH resources.

Traci Mondoro, health science administrator of the NHLBI Blood Resources Program, observed that high-risk ideas or therapies for uncommon disorders that frequently do not attract private sector investment, such as hematologic diseases, would be among NHLBI target projects.

NIEHS RAID priorities, according to Dennis Lang, deputy director of extramural research and training, include environmental components of childhood asthma, allergies, and cardiovascular diseases, as well as research related to countering potential terrorist activities or, as described at the NIH-RAID website: "development of new therapeutic approaches for treating or preventing injury and disease caused by the intentional release of chemical agents by terrorists."

For an overview of each institute's RAID research priorities, visit **<http://nihroadmap.nih.gov/raid>**.

Overall, Briggs commented, "projects will usually not be therapies for very common disease[s] because, by and large, these topics are being addressed by private industry." But she added that there could well be exceptions to that generalization, such as research involving a therapy that cannot attract private sector support because property protection is considered inadequate.

"The focus will not just be on rare diseases but on conditions where we think there is a roadblock," she said.

While the number and kind of proposals remain to be seen, "there has been a discussion about antibiotics for unusual infections and protein-folding chaperone molecules that might treat genetic diseases that result in impaired protein processing, as two possible examples," Briggs said.

The two-year pilot RAID program will fund about 8 to 10 projects a year. "One measure of the success of the program," Briggs noted, "will be whether it can get the projects into early clinical testing." ■

GETTING TO THE CORE

	Preliminary Request Submission Date	Preliminary Evaluation Notification	Full Proposal and Request Submission Date
Cycle 1	February 1, 2005	March 8, 2005	May 2, 2005
Cycle 2	June 1, 2005	July 6, 2005	September 1, 2005
Cycle 3	January 2, 2006	February 6, 2006	April 3, 2006
Cycle 4	June 1, 2006	July 6, 2006	September 1, 2006

Selected* NIH Intramural Research Accomplishments 2004

Add to the body of knowledge about normal and abnormal biological functions and behavior

Identification of disease genes

■ Variants in a single gene on chromosome 20 (hepatocyte nuclear factor 4α, or HNF4α, a transcription factor that influences insulin response to glucose) found to confer a 35 percent increased risk of type 2 diabetes in Finnish populations (NHGRI)

■ Identification of two genes through microarray screening— *ezrin* and *SIX1*—that regulate the metastatic phenotype of rhabdomyosarcoma cells in mouse models, suggesting the possibility of clinical interventions to prevent metastasis (NHGRI, NCI)

■ Identification of five chromosomal regions that harbor attention-deficit hyperactivity disorder susceptibility genes (4q13.2, 5q33.3, 8q11.23, 11q22, and 17p11) (NHGRI, NIMH)

■ A polymorphism in the serotonin transporter gene found to be associated with anxiety and a risk for depression in the face of adversity in female, but not male, rhesus monkeys, possibly helping to explain the increased incidence of certain stress-related disorders in women (NIAAA)

■ The cloning of dardarin (*LRRK2*), a new gene for Parkinson's disease, mutations in which cause autosomal dominant Lewy body disease and account for approximately 5 percent of cases (NIA)

■ A new Fanconi anemia gene for FANCB, the only one transmitted in a sex-linked manner, identified through biochemical techniques that recovered components of the purified complex of interacting Fanconi proteins (NIA)

■ Identification of a polymorphism in the promoter of the *CYP2J2* gene that increases the risk of coronary artery disease, the first evidence of disease relevance for this P450 gene (NIEHS)

■ Identification of a variant in a gene that governs the activity of the brain chemical messenger glutamate that increases the risk for schizophrenia; the gene codes for the glutamate receptor GRM3, which is responsible for regulating glutamate in synapses (NIMH)

Important new animal models

■ A transgenic mouse model with reduced levels of Notch protein exhibited impaired communication at neuronal synapses in the hippocampus critical for learning and memory but responded to Notch activation by another protein, suggesting Notch as a new target for therapeutic interventions to improve learning and memory (NIA)

■ Development of a natural-challenge mouse model for plague infection and testing of an experimental plague vaccine that proved to be 100 percent effective; the model will be used to test other plague vaccines in development and to track the spread of plague bacteria through a host to study possible therapeutic interventions (NIAID)

■ Development of a mouse model of SARS replication that demonstrated that mice produce neutralizing antibodies to the SARS virus that protect them from re-infection and that immune sera from infected mice protected other mice from SARS infection; thus far, the mouse model has been used to demonstrate the efficacy of a DNA vaccine, an inactivated vaccine, a vectored vaccine, and three candidate immunotherapies (NIAID, CC)

■ A small dose of cholera toxin protected a rodent model of uveitis from developing the disease (by countering the Th1 immune response), offering proof of concept for an immunomodulatory approach to this autoimmune disease that may prove a safer alternative to chronic administration of immunosuppressive agents (NEI)

■ Improved heart function after ischemia-reperfusion injury in transgenic mice with cardiac-specific overexpression of the heart enzyme CYP2J2—pointing for the first time to an endogenous role for this enzyme in the heart, with implications for the treatment of ischemic heart disease (NIEHS)

■ Injection of a glutamate receptor agonist into the ventral tegmental area of the brain diminished contextual cue–induced relapse to heroin seeking in a rat-relapse model, suggesting that group II metabotropic glutamate receptors be targeted in the treatment of relapse to heroin and other drugs of abuse (NIDA)

■ Discovery and evaluation of a novel dopamine D3 receptor antagonist—the first water-soluble compound in its class—in animal models of cocaine abuse to elucidate the role of D3 receptors in drug reinforcement (NIDA)

Basic discoveries in cell, molecular, and structural biology with implications for the treatment of human disease

■ Advances in understanding the developmental pathways involved in bone and joint formation, namely, the balanced interplay in Wnt signaling that results in osteoblast tissue that eventually becomes segments of bone separated by regions of cartilage that become joints (NHGRI)

■ Identification of two novel mechanisms that allow human antibodies to overcome HIV-1's defenses and enhance recognition of the virus, thus providing new targets for HIV-1 vaccines and therapeutics (VRC)

■ Demonstration that CCR5-tropic HIV preferentially infects certain dendritic cell populations, possibly enhancing infection, contributing to immune evasion, and providing a selective advantage for CCR5-tropic virus that may explain its preferential transmission in nature (VRC)

■ Enhanced oligodendrocyte progenitor differentiation found to promote remyelination, suggesting that drugs designed to target the sigma-1 receptor may be useful in treating demyelinating diseases or other myelination-related pathopsychiatric disorders (NIDA)

■ Identification of the basolateral complex of the amygdala as a key factor in environmental triggers of drug-induced brain reward and therefore a key target for antirelapse therapies for alcoholism and drug addiction—hitherto poorly understood and poorly treatable (NIDA)

■ Elucidation of the underlying mechanism of mental retardation in Down's syndrome through the finding in Drosophila that overexpression mutants in the homologous relevant human region results in severe learning defects induced by biochemical alterations, not by maldevelopment of the brain (NINDS)

■ Use of the hunger hormone ghrelin found to inhibit proinflammatory cytokine expression upon immune activation in vitro and within in vivo sepsis models; strategies to treat human inflammatory and autoimmune disorders might be entertained (NIA)

■ The finding that autophagy is a key immune cell death mechanism and is, paradoxically, induced by inhibiting one of the very enzymes that initiates apoptosis, caspase-8—along with the identification of *beclin1* and *ATG7* as key genes involved in autophagy—suggests the protein products of these genes as targets for drug discovery in the effort to inhibit this form of cell death; awareness of this previously unrecognized pathway may also aid in the design of treatments for autoimmunity (NIAID)

■ Identification of critical basic molecular mechanisms whereby small GTP-binding proteins of the Rho family coordinate rapid changes in cell shape, motility, and overall cytoskeletal function with the nuclear expression of growth-related genes involved in both normal and cancerous cell growth (NIDCR)

■ Demonstration that estrogen promotes angiogenesis and tumor growth by downregulating a naturally occurring soluble "decoy" protein, suggesting that inhibition of sVEGFR-1 expression represents a novel mechanism of an estrogen-driven "angiogenic switch" that is responsible for breast carcinoma progression (NIDCR)

■ Demonstration that SLPI, a protease inhibitor in mucosal secretions, inhibits HIV from infecting macrophages by binding to annexin 2, a newly recognized HIV cofactor (NIDCR)

■ The discovery that human cells can splice proteins, strongly enhancing the understanding of protein antigens and T-cell immunology (NCI, NIAID)

■ Demonstration that growth factors

** For this year's IRP research roundup, IC scientific directors were asked to limit their selections to four to six "discoveries/new models/new tools reported in 2004 that . . . most advance the knowledge base in the field or have a significant impact on diagnosis, prevention, or treatment of heretofore poorly understood conditions or conditions that are important from a public health standpoint . . . . [also] clinical trials of new therapies/strategies launched in 2004 that address the types of conditions noted above."*

interleukin-2 and interleukin-15 have contrasting roles in the life and death of lymphocytes, which allows understanding of the maintenance and survival of T cells that confer long-term specific memory immune response (NCI)

■ Infusions of nitrite ions into several mammalian species shown to induce production of nitric oxide and resultant blood flow changes, suggesting that pharmacological use of nitrite solutions for various diseases may be possible (NIDDK, CC, NHLBI)

■ Demonstration that the mouse X chromosome is enriched for all genes preferentially expressed in sexually dimorphic tissues (such as the uterus, ovaries, prostate), thereby reconciling all previously published data on this subject from flies, worms, mice, and humans (NIDDK)

■ Shuffling the prion domain of Ure2p (randomizing the amino acid sequence without changing the amino acid content) found to produce sequences that can still form prions (NIDDK, NIAMS)

■ Demonstration through mutation studies and quantum chemical calculations that Ser113 of heat shock protein 90 (HSP90) is critical for the binding of the anticancer compound geldanamycin to HSP90 (NCI, CIT)

■ Overexpression of the enzyme Cdk5 found to decrease the activity of the Src enzyme and inhibit cell migration and wound closure in corneal epithelium, suggesting a new approach for treating persistent corneal ulcers and other conditions with impaired wound healing (NEI)

■ Discovery that adiponectin, an adipokine secreted by adipose cells, directly activates endothelial nitric oxide synthase and stimulate production of nitric oxide in vascular endothelial cells, providing a molecular basis for the ability of adiponectin to improve insulin sensitivity and oppose accelerated atherosclerosis in diseases associated with insulin resistance (diabetes, obesity, hypertension, dyslipidemias, and coronary heart disease) (NCCAM)

■ First report to demonstrate that it is the human pregnane X receptor that mediates induction of the drug-metabolizing enzyme CYP2C9 by rifampicin, phenobarbital, and hyperforin (found in St. John's wort), explaining how concomitant exposure with certain prescribed drugs (such as anticoagulatory, antidiabetic, and antihypertensive agents) leads to increasing the rate of disappearance of drugs and compromised efficacy (NIEHS)

■ Endocannabinoids demonstrated to tonically suppress cardiac contractility in hypertension and to normalize blood pressure in three different models of experimental hypertension, suggesting the endocannabinoid system as a novel therapeutic target in hypertension (NIAAA)

■ Interleukin-6 found to ameliorate alcohol- and obesity-associated fatty liver disease and to prevent ischemia-reperfusion injury of fatty livers, suggesting therapeutic potential for IL-6 in human fatty liver disease (NIAAA)

■ Interleukin-22, a T cell–derived cytokine, demonstrated to be a novel hepatoprotective cytokine that may have therapeutic potential in treating acute liver failure (NIAAA)

■ Establishing that a major role of WRN, the protein found to be deficient in Werner syndrome (WS), is at the telomere end, where it functionally interacts with other telomere proteins and where it participates in maintenance and repair, the lack of which leads to genomic instability, a key feature of WS cells (NIA)

■ Determination of a series of high-resolution structures of sequence-specific as well as nonspecific endonucleases, thereby resolving the dilemma of substrate specificity and metal ion requirement and gaining insights into DNA repair, phage restriction, retroviral replication, and integration (NIDDK, NICHD)

■ Evidence from a decade-long MRI study of normal brain development from ages 4 to 21 that the prefrontal cortex, the center of reasoning and problem solving, is among the last areas of the brain to mature and does not fully develop until young adulthood (NIMH)

■ Findings suggesting that the basal ganglia are involved in both initiation and suppression of saccadic eye movements in complex behavioral contexts (NEI)

■ Elucidation of the role of brain-derived neurotrophic factor in synapse formation and in achieving long-term hippocampal plasticity (NICHD)

■ Findings in an ex vivo human lymphoid tissue system that suggest that triggering in vivo HIV viral production in latently infected cells in combination with therapies may become a meaningful strategy to purge latent viral reservoirs (NICHD)

■ Enhanced understanding of the kainate receptor gene family: solving the structures of the GluR5 and GluR6 ligand-binding cores, demonstrating that kainate receptor efficacy is controlled by domain closure, and elucidating their slow recovery from desensitization (NICHD)

■ Further elucidation of the role of mammalian mitochodrial fission and fusion mediators in apoptosis (NINDS)

■ Demonstration that multivesicular release at mammalian ribbon synapses is coordinated among release sites (NINDS)

Develop new or improved instruments and technologies for use in research and medicine

Advances in imaging

■ Development of an automated, fault-tolerant system to enhance high-throughput NMR protein structure determination (CIT, NIDDK, NCI, NHLBI)

■ Development of a novel functional MRI technique for measuring cerebral blood volume, blood flow, and blood oxygenation signals in a single scan (NIDA)

■ Demonstration that MRI can detect single particles (single, micrometer-sized iron oxide particles) and that single-particle detection should prove useful for cellular imaging (NINDS, NHLBI)

■ Development of a dynamic micro–magnetic resonance mammolymphangiography method to visualize lymphatic flow from breast tumor tissue to draining lymph nodes to identify a sentinal lymph node and determine the presence or absence of nodal involvement; this approach may provide surgeons with a precise map of involved and uninvolved lymph nodes (NCI, NIDDK)

■ Development of the technique of picosecond time-resolved X-ray crystallography, achieving stunning agreement with molecular dynamics simulations (NIDDK)

■ The use of atomic force microscopy to visualize individual rhodopsin molecules (a key vision signal transduction protein) in native disk and reconstituted membranes, providing a foundation to study medically important proteins in biological membranes, with possible applications in nanotechnology (DBEPS, NIAAA)

■ Novel fluorescence and photoactivatable imaging tools to document that the behavior of chromosomes, cytoskeleton, and Golgi during mitosis is coordinated through the activity of the small GTPase Arf1, elucidating the activity of organelles and raft-associated plasma membrane proteins (NICHD)

■ Identification of a new series of compounds with extremely high affinity for $\alpha 4 \beta 2$ nicotinic acetylcholine receptors (nAChRs) that show promise as imaging agents for extrathalamic nAChRs (NIDA)

■ Development of a new PET radioligand for 5-HT1A receptor to use in the study of the molecular basis of mood disorders (CC, NIMH)

Advances in bioinformatics

■ Implementation of a web-based protocol-tracking system that enables PIs to manage clinical studies as well as monitor review processes, view status changes, and respond to requests for additional information and allows protocol coordinators to manage the entire Institutional Review Board approval process (NINDS, CIT)

Advances in biotechnology

■ Identification of stem cells in human postnatal periodontal ligament that regenerate cementum-like and periodontal ligament–like structures when transplanted into immunocompromised mice; these findings suggest that these easily accessible cells may be useful in repair of periodontal tissue (NIDCR)

■ Development of a simple plasmid transfection method for efficient intracellular production of papillomavirus-based gene transfer vectors utilizing the viral L1 and L2 proteins; the availability of high-titer papillomavirus vector stocks should facilitate future studies of papillomavirus replication and tropism, and the vectors may have future utility as vaccine or gene therapy vehicles (NCI)

■ Demonstration that highly proliferative

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precursor cells for islets of Langerhans can be generated from cadaver pancreases and then redifferentiated in cell culture (NIDDK)
- Development of new pepitomimetic ligands for integrin targeting that will provide a new approach for targeted delivery of nanoparticles into human vasculature (CC)

Develop new or improved approaches for preventing or delaying the onset or progression of disease and disability
- Genetic counseling shown to improve adherence to recommendations for colon cancer screening and prevention in both mutation-positive and mutation-negative individuals in families with hereditary nonpolyposis colorectal cancer, supporting the clinical practice of genetic susceptibility testing (NHGRI, NCI, NNMC)
- Dietary fiber intake, especially from grains, cereals, and fruit, found to lower the risk of colorectal adenoma among individuals enrolled in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (NCI)
- Determination that breastfed babies in the United States have a 20 percent lower chance of dying between one month and one year of age across all causes of death, including the most common at that age—SIDS, infections, and trauma; about 720 deaths could be prevented if all children under one were breastfed (NIEHS)
- Finding that asthmatic children with a genetic deficiency of glutathione S-transferase M1GSTM1 may be more susceptible to the deleterious effects of ozone on the small airways and might derive greater benefit from antioxidant (vitamins C and E) supplementation (NIEHS)
- The finding that intake of fiber, specifically from fruits and soy products, is related to a decreased risk of developing persistent cough with phlegm production (NIEHS)
- Decreasing levels of free testosterone among men enrolled in the Baltimore Longitudinal Study on Aging found to predict increased risk of developing Alzheimer's disease (NIA, NCCAM)
- The first direct experimental demonstration in humans that calorie restriction increases psychoactive drug self-administration, using cigarette smoking (nicotine) as the drug (NIDA)
- Establishment that exposure to benzene at levels even lower than the U.S. occupational standard of 1 part per million results in lowered white blood cell and platelet counts, with especially marked effects on progenitor cell colony formation; individuals with genetic variants in two metabolizing enzymes—myeloperoxidase and NAD(P)H:quinone oxidoreductase—identified as especially susceptibility to benzene hematotoxicity (NCI)
- Establishment of the magnitude of risk for subsequent uterine cancer among breast cancer patients treated with tamoxifen who survived 5 years or more: an 8-fold relative risk of rare but aggressive malignant mixed müllerian tumors, as well as a 2.3-fold risk for endometrial adenocarcinoma (NCI)

Vaccine development
- Development of a recombinant DNA vaccine against SARS coronavirus that induced neutralizing antibodies in mice; a Phase I clinical trial is underway (VRC)
- Phase I clinical trials at various stages to evaluate the safety and immunogenicity of a DNA vaccine against Ebola virus in adult volunteers, a recombinant adenoviral vaccine against multiple clades and genes of HIV-1 in uninfected adult volunteers, and a six-plasmid DNA vaccine against multiple clades of HIV-1 in uninfected adult volunteers (VRC)
- Ongoing clinical trials, in Baltimore and Costa Rica, of an HPV 16 (human papillomavirus type 16) L1 virus-like particle vaccine to prevent cervical cancer (NCI)

Develop new or improved methods for diagnosing disease and disability
- Development of a "lab-on-a-chip" rapid immunoassay for the measurement of hormones in real time, enabling rapid patient assessment with minimal intervention during other clinical or surgical procedures (DBEPS, NICHD, NIDDK)
- Development of a minimally invasive sample procurement needle, based on a 32-gauge acupuncture needle, enabling in vivo sampling of skin, muscle, or other organs while causing no discomfort beyond that associated with acupuncture (DBEPS, NCI, NIAMS)
- Development of a new microanalytic technique to distinguish patients with and without painful myofascial trigger points through continuous myofascial fluid sampling (CC)
- Temporarily disabling dopamine receptors in monkeys' brains found to result in the performance of all tasks as if a reward were anticipated for each one, suggesting that highly specific manipulations of brain receptors could be a useful approach in discerning the molecular mechanisms that control other cognitive functions (NIMH)
- Brain imaging to pinpoint the site of a defect in a brain circuit associated with a specific thinking deficit in Williams syndrome, a rare genetic disorder, offers clues on how genetic flaws may translate into cognitive symptoms in more common and complex major mental disorders (NIMH)
- Identification of an area near the left temple of the monkey brain as the site of processing species-specific vocalizations suggests that this is not only a higher-order auditory processing area but also one that is a precursor for acoustic language circuits in humans (NIMH, CC)
- The finding that an emotion-regulating brain circuit is overactive in people prone to depression and that depression relapse is induced by a depletion of tryptophan, the chemical precursor of serotonin, suggests that tryptophan depletion unmasks an inborn trait associated with depression and that a genetic predisposition to inadequate serotonin activity may be at the root of the mood disorder (NIMH, CC)
- The finding that couples diagnosed as clinically infertile due merely to not having achieved pregnancy after a year of trying (without additional clinical indicators of reproductive dysfunction) should continue attempting for up to two years before considering potentially risky assisted reproductive technologies (NIEHS)

Gene expression patterns
- Development of an expression microdissection instrument that facilitates more rapid and precise genomic and proteomic analysis (NCI, NICHD, CIT)
- Development of a novel model for quantitatively analyzing cell cycle gene expression that promises enhanced understanding of tumor cell growth and the effects of genotoxic agents on specific cell cycle checkpoint genes (NIEHS)
- Identification of transcription factor nuclear factor–kappa B (NF-κB) as an important modulator of the altered gene expression profile and malignant phenotype in squamous carcinoma; inactivation of NF-κB inhibited malignant phenotypic features, including proliferation, cell survival, migration, angiogenesis, and tumorigenesis (NIDCD, NCI)
- Patterns of genes active in tumor cells shown to predict whether patients with diffuse large B cell lymphoma are likely to be cured by chemotherapy, suggesting that gene expression profiling may facilitate clinical treatment options for standard or other therapies (NCI)
- Identification of a target RNA motif for RNA-binding protein HuR by immunoprecipitation of HuR-RNA ribonucleoprotein complexes, cDNA array analysis of target RNAs, and elucidation of the primary and secondary structures of the bound transcripts (NIA)
- Continuing development of a microfluidic, flow-through immunoassay for simultaneous quantification of multiple proteins in submicroliter samples; advantages over existing array technology include protein detection by single-point capture and reusable capture antibodies (DBEPS, CIT)

Develop new or improved approaches for treating disease and disability
- Clinical trial evidence that retroviral gene therapy yields gene-corrected lymphocytes and clinical improvement in patients with X-linked severe combined immunodeficiency disorder who have failed standard bone marrow transplant and have no other therapeutic options (NHGRI, NIAID)
- A clinical trial of humanized anti-CD25 (daclizumab, developed in the NCI intramural program) shown to inhibit disease activ-

Recently Tenured

Nilanjan Chatterjee *was trained in mathematical statistics at the Indian Statistical Institute, Calcutta, and received a Ph.D. in statistics from the University of Washington, Seattle, in 1999. In his thesis, he developed efficient methods for analyzing data from two-phase studies in which inexpensive exposure information is collected on a relatively large number of phase I subjects and more expensive exposure data are collected on a smaller subset of efficiently selected subjects. Chatterjee joined NIH as a research fellow in the Division of Cancer Epidemiology and Genetics (DCEG), NCI. Since 2001, he has been a principal investigator in the Biostatistics Branch.*

Fran Pollner

Nilanjan Chatterjee

Advances in molecular and cellular technologies have given epidemiologic researchers new opportunities to study the pathogenesis of complex diseases through population-based studies. The advent of these data in epidemiologic studies also has given rise to challenging theoretical and methodological problems in statistics. In recent years, I have initiated methodologic projects in three major areas of molecular epidemiologic studies, including *gene-environment interactions, genetic association, and etiologic heterogeneity* of diseases using molecular and pathologic markers.

It is now thought that the risks of many complex diseases are determined by the joint effect of genetic susceptibility and environmental exposures, and study of the interplay of these two factors can greatly enhance our understanding of the etiology of these diseases. Because studies of interactions, especially for rare exposures, typically require a large sample size, efficient designs and analytic principles for gene-environment interaction studies are an important area of epidemiological and statistical research.

I have shown how the power of case-control studies to detect gene-environment (G-E) interactions can be increased under the assumption that genetic and environmental risk factors are independently distributed in the underlying source population. In one manuscript, I presented a general likelihood framework for exploiting the G-E independence for population-based case-control studies of unrelated subjects.

In a second manuscript, I presented a conditional likelihood framework for analysis of family-based or other type of matched case-control studies. My framework relies on a relatively weak within-family (or within matched-set) G-E independence assumption, rather than independence in the entire population.

One of my long-term research goals is to study efficient design and analytic methods for using single nucleotide polymorphisms (SNPs) to detect disease susceptibility genes. Once the SNPs to be studied have been selected and genotyping has been completed, an important issue is how to analyze data efficiently on multiple SNPs within a genomic region.

It has often been argued that haplotype-based association analysis can be powerful for this purpose, because haplotypes can capture interactions between SNPs as well as association due to linkage disequilibrium of the genotyped SNPs with untyped causal variant(s) in the same region. I have collaborated with Jinbo Chen in developing methods for haplotype-based genetic association studies in the context of cohort and nested case-control studies. Previous methods for haplotype analysis relied on binary logistic regression models. We have developed methodologies for testing and estimation in the Cox proportional hazard model that is more appropriate for analysis of prospective cohort-based studies.

It is becoming increasingly clear that many cancers (and other complex diseases) show phenotypic variation, yet the standard approaches for etiologic analysis do not readily allow for the evaluation of risk factors in relation to disease heterogeneity. Besides traditional pathologic data, such as stage, histology, and grade, various molecular technologies are now increasingly available for disease classification.

Analogous to multivariate statistical methods for the study of multiple interrelated risk factors, I have developed a method for risk factor evaluation in relation to multiple interrelated disease characteristics. The method has proven useful in a series of studies to identify heterogeneity in the effect of various genetic and environmental risk factors on the size, histologic characteristics, and multiplicity of adenomatous colorectal polyps.

All of my work has been directly or indirectly motivated by collaboration with my epidemiologist colleagues at the DCEG. My training in mathematical statistics and the scientific environment of DCEG have yielded a rich statistical research program for modern epidemiological studies.

ity (both on imaging and in daily activities) in multiple sclerosis patients not responding to interferon-β, the standard therapy (NINDS, NCI)

■ A novel magnetic resonance imaging biomarker identifies blood-brain barrier disruption early enough in the course of stroke-induced ischemia and reperfusion to inform decisions regarding adjunctive therapy to reduce complications associated with acute thrombolytic therapy (NINDS)

■ Evidence supporting the potential role of regulatory T cells in the diminution of HIV-specific immune responses in HIV-infected individuals may lead to improved therapeutic and vaccination approaches designed to enhance or elicit HIV-specific immune responses (NIAID)

■ Monoclonal anti-IL-12 proved to be an effective treatment of active Crohn's disease in an early-phase clinical trial, paving the way for a phase III trial in a large patient cohort; the trial also provided solid proof that a Th1 process is the final common T-cell pathway of inflammation in Crohn's disease (NIAID)

■ Allogeneic T lymphocytes from a genetically matched donor found to induce tumor regression in patients with metastatic breast cancer—demonstrating for the first time that a graft-vs-host tumor effect may have therapeutic value in metastatic breast cancer (NCI, CC)

■ The launching of a double-blind, placebo-controlled, cross-over trial to determine if dark chocolate (which contains antioxidants, including polyphenol epicatechin) lowers blood pressure and improves insulin resistance and endothelial function in people with essential hypertension—relevant to the treatment of diabetes, obesity, hypertension, and atherosclerosis (NCCAM)

■ Expansion of a clinical study of electroacupuncture for the treatment of delayed nausea and vomiting due to chemotherapy in patients with pediatric solid tumors; the study is now a multicenter study in collaboration with the Children's Oncology Group (NCCAM, NCI)

■ The launching of the first clinical study of a mistletoe-chemotherapy (gemcitabine) combination in patients with advanced solid tumors; this phase I trial is a model for the study of botanical-drug interactions in combination regimens for treating cancer (NCCAM, NCI)

■ Launching of the first "proof of principle" clinical trial to test the ability of the CB1 receptor antagonist rimonabant to reduce the desire to drink in heavy drinkers(NIAAA) ■

People

Recently Tenured

Heping (Peace) Cheng *received degrees in applied mathematics and mechanics, physiology, and biomedical engineering from Peking University, China, where he served as a faculty member in the Department of Electrical Engineering before earning his Ph.D. degree in Physiology in 1995 from the University of Maryland in College Park. He joined the NIH Intramural Research Program as a senior staff fellow in 1995 and was selected as a tenure-track investigator in 1998. He is now a senior investigator and the head of the Ca^{2+} Signaling Unit in the Laboratory of Cardiovascular Science, NIA.*

Heping Cheng

In my early years at Peking University, recognizing the power of multidisciplinary integration, my mentors and I devised a unique career path beginning with rigorous training in physiology, mathematics, physics, and computer science. My dream was to pursue fundamental biomedical questions by seamless integration of the philosophy, theory, and craftsmanship of these different fields.

As a Ph.D. student at the University of Maryland, I was fascinated with the economy and simplicity of Ca^{2+} in biological systems. As a divalent cation, calcium undergoes neither catabolism or anabolism, yet it plays pivotal roles in nearly every aspect of biology. This paradox of simplicity and complexity became even more profound as I realized that the list for second messengers at work in any biological system is extremely short—cAMP, IP_3, ROS, for example. What mechanisms bestow Ca^{2+}, or any second messenger, with such amazing signaling specificity and versatility?

In my first English publication, my coworkers and I reported the discovery of "Ca^{2+} sparks" as the elementary events of intracellular Ca^{2+} signaling. Ca^{2+} sparks are brief openings of variable cohorts of from one to eight ryanodine receptor (RyR) Ca^{2+} release channels in the endoplasmic or sarcoplasmic reticulum (ER or SR). The summation of coordinated activation of Ca^{2+} sparks in space and time generates complex global Ca^{2+} signals.

Subsequent research in "sparkology" has unraveled exquisite hierarchal architecture of Ca^{2+} signaling. On the basis of these findings, we have proposed that Ca^{2+} signaling is, in essence, a discrete, stochastic, and digital system, rather than a continuous, deterministic, analog system, as previously thought. This concept not only sheds new light on calcium's complex simplicity, but also allows for unprecedented precision in the detection and definition of disease-related aberrant Ca^{2+} signaling.

In collaboration with M.T. Nelson, we uncovered a novel Ca^{2+} signaling pathway in which sparks *relax* vascular smooth muscles. In this pathway, subsurface sparks activate large-conductance Ca^{2+}-sensitive K^+ channels, which shut off L-type Ca^{2+} influx through membrane hyperpolarization. This leads to reduction of intracellular Ca^{2+} and muscle relaxation. This finding vividly illustrates that a single simple messenger, Ca^{2+}, can serve different and even opposing roles in the same cell.

In heart muscle cells, Ca^{2+} entering through L-type Ca^{2+} channels traverses a 12-nm junctional cleft to activate RyRs in the SR, liberating stored Ca^{2+}. This process is known as Ca^{2+}-induced Ca^{2+} release (CICR). For years, many physiologists dreamed of "seeing" nanoscale, intermolecular CICR. Our team has now painstakingly accomplished the optical recording of single L-type channel Ca^{2+} currents or "Ca^{2+} sparklets." We went on to demonstrate that a single sparklet can trigger a spark in an all-or-none fashion. These steps made it possible to define the stoichiometry, kinetics, and fidelity of intermolecular signaling in real time and in live, intact cells.

Most recently, we found that when a spark ignites, rapid and substantial decreases in Ca^{2+}, called "Ca^{2+} blinks," develop within nanometer-sized stores—the junctional cisternae of the SR. The complementary spark-blink signal pairs in heart may be a prototype for similar reciprocal signals and suggest space-time organization of signaling from Ca^{2+} stores, including capacitive Ca^{2+} entry and ER/SR-dependent apoptotic signaling.

The aims of our current and future Ca^{2+} signaling research are to discover new phenomena, functions, and mechanisms—leading to new concepts and theories—as we develop novel methods, analytic tools, special reagents, and instruments for Ca^{2+} studies. We hope these "nuts and bolts" will broaden the frontier of technology for the field.

We will continue to focus on Ca^{2+} signaling in subcellular compartments and organelles (mitochondria, ER/SR, and nuclei) and in vivo imaging of biosensors at single-cell and single-molecule resolutions. But beyond this, we will consider the Ca^{2+} signalome as a whole, including synthesizing information gleaned from molecules, pathways, subcellular organelles, cells and organisms. This integration enlists the powerful addition of bioinformatics and system theory to our current research portfolio. In addition, through collaboration, we also hope to translate our findings to pertinent disease models, thereby advancing the understanding of the etiology and enlightening the treatment of human diseases.

Karl Csaky *received his M.D. degree in 1983 and his Ph.D. in pharmacology in 1987 from the University of Louisville in Kentucky. Following an internship in Medicine at Duke University in Durham, N.C., he spent 15 months as a Fulbright Scholar in the University Eye Clinic in Essen, Germany, with Gerd Meyer-Schwickerath. He completed his ophthalmology residency at Washington University in St. Louis in 1990 and spent one year as a fellow in the Retinal Vascular Center at the Wilmer Eye Institute, Johns Hopkins Hospital, Baltimore. From 1991 through 1994, he completed a postdoctoral fellowship at the NCI laboratory of Stuart Aaronson. He joined the NEI in 1994 and currently heads the Section on Retinal Diseases and Therapeutics.*

Age-related macular degeneration (AMD) is the leading cause of blindness in patients over the age of 60 years in the United States. It is estimated that 1/3 of all people over the age of 75 will develop AMD.

AMD has three major clinical presentations: the early dry form, which is characterized by extracellular deposits under the retina; the severe dry or atrophic form in which retinal cells undergo apoptosis; and the wet form, where neo-vascularization develops in the normally avascular sub-retinal space, so-called choroidal neovascularization (CNV).

My laboratory and clinical efforts are focused on elucidating the pathogenesis and developing new therapies for all three forms of AMD. As a clinician-sci-

entist, much of the focus in my lab is on research that has direct disease relevance, drawing insights from clinical presentations or therapeutics that can be taken into clinical trials.

For example, in the atrophic form of AMD, it is known that cell death begins in one unique cell layer of the retina termed the retinal pigment epithelium (RPE). The RPE is a nonrenewable cell that maintains retinal function from birth through death. However, the natural history of RPE cell death in patients is one of an end-stage phenomenon that occurs late in the course of AMD. Therefore, we hypothesized that RPE cell apoptosis might be different from apoptosis in cells which undergo a more rapid time course of cell death.

Ernie Branson

Karl Csaky

Indeed, we discovered that unlike immune cells, RPE cells use primarily the release of apoptosis-inducing factor (AIF) .and not activation of caspases to modulate cell death. In addition, the RPE cell has unique mechanisms for self-protection from various insults. After an oxidative injury, for example, a microarray profile of RNA expression in RPE cells demonstrated activation of both antioxidative defense mechanisms as well as direct downregulation of proapoptotic pathways. We are now studying how the loss of these survival mechanisms interplays with AIF and how this process may be involved in the development of the late atrophic form of AMD.

In examining the development of the neovascular form of AMD in various animal models, my laboratory discovered that bone marrow–derived endothelial cells (EPCs) are involved in this process. A key question about this and other forms of neovascularization is whether EPCs have some important role in this process. We hope to answer this question in part by examining EPCs from patients with neovascular AMD.

Unlike neovascularization in other diseases, such as cancer or cardiac ischemia, development of CNV can be precisely documented through multiple imaging techniques showing rates of growth, extent of growth, phenotypic characteristics and various aspects of blood flow. In fact, when we analyze various characteristics of neovascularization in AMD patients, we find a large variety of clinical presentations. We hope to determine, from patients, specific functions of circulating EPC's and correlate these to the various phenotypes of neovascularization. Our goal is to develop a predictive and therapeutic blood test to identify patients most at risk for aggressive neovascularization.

Because only a small amount of tissue needs to be treated in patients with AMD, my laboratory is also involved in targeted sustained drug delivery through the use of drug implant delivery systems. We have developed a novel implant device that can deliver various antiangiogenic agents for up to three years. Clinical trials of these devices are now being planned.

In another study of neovascular AMD, in collaboration with Scott Cousins at the University of Miami, we identified the importance of innate immunity in the development of CNV in animals. This led us to develop a therapy by optimizing a steroid formulation that could be injected into the eye. This novel formulation has been produced and successfully injected into patients and is now in Phase I and II trials at NIH. A multicenter Phase III trial using this steroid formulation is now underway in 300 patients with neovascular AMD.

Peter Inskip

If the results of these trials are positive, they will be used for a new drug application through the FDA. Thus, beyond its direct translation from lab to clinic, our work is giving us useful insights into FDA regulatory issues and the economics of drug development.

Peter Inskip *received his Sc.D. in epidemiology from the Harvard School of Public Health in Boston in 1989. He then joined NCI as a fellow in the Division of Cancer Epidemiology and Genetics (DCEG). In 1995, he left NCI to take a position as associate professor at the Texas A&M College of Veterinary Medicine in College Station. He returned to NCI in 1998 and is currently Senior Investigator in the Radiation Epidemiology Branch of DCEG.*

My research focuses primarily on quantifying radiation-related cancer risks and clarifying susceptibility factors that influence these risks. For example, I am conducting studies of therapy-related second primary cancers in a population of more than 14,000 five-year survivors of childhood cancer diagnosed between 1970 and 1986.

These studies include detailed information on radiotherapy and chemotherapy and anatomic site–specific radiation dosimetry. Our analyses have demonstrated very large relative risks for second neoplasms of the thyroid gland, brain, and breast due to radiotherapy. Interestingly, risk of thyroid cancer increased with dose at low to moderate doses but declined at very high doses, probably due to cell-killing effects of high-dose radiotherapy on the thyroid gland.

Although relative risks associated with radiotherapy for childhood cancer are very large, most patients who receive high partial-body doses of radiation do not develop a second cancer. It is unclear to what extent this is random or dependent on differences in host susceptibility. We are evaluating whether polymorphisms in genes involved in DNA protection, DNA repair, cell-cycle control, and apoptosis are predictive of second cancer risk.

In an earlier study of nearly 13,000 women treated with radiation for benign gynecologic disorders between 1925 and 1966, I found radiation-related excesses of acute and myelocytic leukemias but not chronic lymphocytic leukemia, Hodgkin or non-Hodgkin lymphoma, or myeloma.

Radiation dose-response relationships also were apparent for cancers of the bladder, colon, and ovary but not for cancers of the uterus or rectum, which appear to be relatively radioresistant organs.

I also am studying cancer risks associated with lower-dose protracted or fractionated radiation exposures. Taking advantage of unique features of the Swedish health-care system, I evaluated the risk of thyroid cancer associated with lifetime history of diagnostic X-rays based on medical records; no association was found. In one of the first systematic studies of cancer among Chernobyl clean-up workers, we found

People

Recently Tenured

no excess of leukemia among 4,833 Estonian clean-up workers followed through 1993. We have expanded the study to include an additional 12,500 workers from Latvia and Lithuania and are extending the follow-up to further evaluate leukemia and solid cancers.

When the public became concerned that radiofrequency radiation emitted by cellular telephones might cause brain cancer, I initiated a case-control study to explore a wide range of hypotheses about the etiology of these poorly understood and often fatal tumors. Our article in the *New England Journal of Medicine* reported no evidence of increased risk of glioma, meningioma, or vestibular schwannoma associated with use of cellular phones. Unlike ionizing radiation, nonionizing radiation shows little evidence of causing cancer.

Cellular telephones might not cause brain tumors, but something does. The etiology of brain tumors has become my second major research focus.

In our study of brain tumors, we observed a significant inverse association between the risk of glioma and history of allergies—a finding that has been confirmed in subsequent studies.

A surprising observation was the lower risk of glioma among left-handed compared with right-handed individuals, which, if not due to chance, may relate to a longstanding hypothesis that prenatal exposure to high testosterone levels affects the developing brain and thymus, resulting in an "anomalous" pattern of hemispheric dominance associated with left-handedness, developmental language disorders, and immune dysfunction.

Glioma incidence was also positively associated with age at menarche and inversely associated with age at first live birth. To follow up on these observations, I am collaborating with other NCI investigators to explore associations of brain cancer risk with genetic polymorphisms involved in inflammation, immune response, and hormonal pathways. We also are studying brain tumor risk with respect to occupational exposures, including solvents, lead, and pesticides.

Because brain tumors are rare, and no single existing epidemiologic study of brain tumors has adequate statistical power to evaluate gene-environment or gene-gene interactions, it is important to combine results from multiple studies of brain tumors.

Towards that end, I organized a workshop that launched an international consortium of investigators conducting etiologic studies of brain tumors. Our aim is to establish a network that will enable investigators to collaboratively address etiologic hypotheses that otherwise could not be studied effectively.

Caroline Philpott *received her M.D. from Duke University, Durham, N.C., in 1987. Following an internal medicine residency at the Johns Hopkins Hospital in Baltimore, she joined NICHD in 1990 and became a clinical associate in the Genetics, Cell Biology, and Metabolism Branch. In 1998, she joined NIDDK, where she is currently a senior investigator in the Liver Diseases Branch.*

Fran Pollner

Caroline Philpott

I am interested in how cells take up and use iron, which is important for human health in a number of ways.

Worldwide, iron deficiency is the most common nutritional disorder, and yet genetic forms of iron overload are also very common. We are only beginning to understand the role that iron plays in the chronic neurodegenerative diseases, such as Friedreich ataxia and Parkinsonism. Pathogenic microorganisms must overcome the iron-withholding systems of the human host to establish infection. These systems are our first line of defense against microbial invaders, and microbial iron uptake mechanisms that overcome these systems are often important virulence factors.

Almost every organism on the planet requires iron because of its versatility in picking up and releasing electrons. This reliance on iron comes at a cost, however, because the same properties that make iron useful also make it very chemically reactive and potentially damaging for cells. Think of iron as cellular dynamite—useful, but dangerous.

Cells use iron to build heme and iron sulfur clusters, which are inserted into a variety of enzymes that carry out essential functions, such as respiration; sterol, lipid, and amino acid biosynthesis; and DNA repair. Most of the iron inside a cell is in the reduced form, which can catalyze the formation of damaging free radicals. Cells face a bioavailability problem with iron, as most iron in an oxygen-containing environment is in the oxidized form, which forms large, insoluble polymers with oxygen and water—rust. Thus, all organisms have evolved sophisticated mechanisms to control the uptake and use of iron.

We began our studies in the one-celled eukaryote *Saccharomyces cerevisiae*, an excellent organism in which to understand basic processes of both eukaryotic cells and pathogenic fungi. We used cDNA microarrays to ask the question "How do cells respond to iron deficiency?" Our studies of the transcriptional response allowed us to identify the set of genes involved in the primary response to iron deficiency and to understand the cell's strategy for surviving iron deprivation. We found that the cellular response took three forms: 1) increasing the expression of iron uptake systems, 2) mobilizing stored iron, and 3) adjusting cellular metabolism to conserve iron.

We identified a new fungal system for iron transport that relied on the uptake of siderophores, which are small molecules that chelate iron. Most bacteria and fungi secrete these compounds in their iron-free form and take them back up once they contain bound iron. Budding yeast don't make siderophores, but they readily take up those made by other microbes.

Siderophore uptake occurs through a family of transporters that exhibit a unique intracellular trafficking pattern that is controlled by the presence of the siderophore substrate. We found that the transporter itself contained a domain that acted as the receptor for siderophores. Binding of siderophores to this domain affected the cellular trafficking of the transporter, directing it to the cell surface only when the appropriate siderophore substrate was available. The regulated intracellular trafficking of transporters has emerged as an important mechanism for controlling transport of many molecules in various cells. We hope to uncover the processes that control the trafficking of transporters in yeast.

One surprising finding of our studies in yeast was how cells adjust to dwindling levels of iron. At first glance, one

might suppose that cells simply continue to use iron in their iron-containing proteins until they run out. But we found that far more sophisticated adjustments take place.

As iron is depleted, yeast turn off transcription of certain nonessential pathways that rely on iron-sulfur cluster proteins and turn on transcription of parallel iron-independent systems. For example, yeast can either synthesize biotin from intermediates, or take it up from the medium. Synthesis requires iron, but uptake does not. Under iron deficiency, biotin synthesis is switched off and uptake is switched on.

Heme utilization is also adjusted in iron deficiency. As cells become iron depleted, they synthesize a heme-degrading enzyme, and this degradation of heme serves two purposes. First, iron is released and reused, and second, heme-dependent transcription is decreased. Heme is an important regulatory molecule, and the degradation of heme results in the downregulation of many proteins that contain iron-rich complexes.

We don't yet know what types of adjustments are made in human cells in response to iron depletion. A new focus of our lab is to use yeast to identify new human proteins involved in iron homeostasis. Yeast and human cells have some clear differences in how they take up and use iron, and by selecting human genes that confer new iron-handling properties on yeast, we hope to identify novel human genes of iron metabolism.

Brant Weinstein *received his Ph.D. from the Massachusetts Institute of Technology, Cambridge, Mass., in 1992. After completing his postdoctoral work at the Massachusetts General Hospital, Boston, he joined the Laboratory of Molecular Genetics, NICHD, in 1997. He is currently a senior investigator in that lab and head of the Unit on Vertebrate Organogenesis.*

My laboratory is trying to understand the cellular and molecular mechanisms responsible for the specification, patterning, and differentiation of blood vessels.

Blood vessels are ubiquitous and vital components of all vertebrates, forming an elaborate network that supplies all tissues and organs with oxygen, nutrients, and cellular and humoral factors. The mechanisms controlling blood vessel growth and regression are still poorly understood, but they have become a subject of intense clinical interest in recent years because of the great promise shown by antiangiogenic therapies for combating cancer.

Fran Pollner

Brant Weinstein

Many of the critical insights into regulation of blood vessel formation have come from developmental studies, and the zebrafish has emerged as an important new vertebrate model organism for investigating early vascular development. This small tropical freshwater fish is genetically tractable and has a physically accessible, optically clear embryo. These features permit noninvasive high-resolution visualization of every vessel in the living animal and simple, rapid screening for even subtle vascular-specific mutants.

Several experimental tools that we developed allowed us to amplify the basic advantages of this system. A microangiographic method for imaging patent blood vessels allowed us to compile a comprehensive atlas of the vascular anatomy of the developing zebrafish. Our transgenic zebrafish lines expressing green fluorescent protein in vascular endothelial cells make it possible to visualize blood vessel formation in intact, living embryos. We devised methods for long-term, multiphoton time-lapse imaging of growing vessels in these transgenic zebrafish and used them to examine the morphogenesis of developing trunk and cranial vessels and adult fin blood vessels.

We used forward genetic mutational screening to identify and characterize zebrafish mutations in developing vasculature. We positionally cloned the defective genes from several vascular patterning mutants, including *violet beauregarde* (defective in *Alk1/acvrl1*), *plcg1*^{y10} (defective in *phospholipase C-gamma-1*), and *kurzschluss* (defective in a novel chaperonin).

We are currently carrying out large-scale genetic screens for chemically induced mutants. These have yielded a large number of new mutations, with phenotypes including loss of all or subsets of vessels, increased sprouting or branching, and vessel mispatterning. Characterization and molecular cloning of these mutants is in progress.

Probably the most fundamental fate choice for endothelial cells is arterial vs. venous differentiation. We were the first to describe a molecular pathway regulating acquisition of arterial-venous identity: sonic hedgehog, vascular endothelial growth factor (VEGF), and Notch signaling, acting in series. Using genetic screening and positional and candidate cloning methods, we identified a mutation in *phospholipase C-gamma–1* leading to defects in angiogenesis and arterial differentiation. We showed that this gene is a major downstream effector of VEGF signaling in vivo. We are currently using microarrays, mutant screens, and other methods to further explore the molecular mechanisms underlying this important cell fate decision.

We are also studying the mechanisms underlying vascular patterning and morphogenesis during development, in particular, how early vascular networks assemble with defined, stereotypic anatomical patterns. We used multiphoton time-lapse imaging of transgenic zebrafish to obtain evidence supporting a novel model for genetically programmed vascular network formation in the embryonic trunk.

Subsequently, we showed that semaphorin signaling— an important mediator of axonal guidance in the nervous system—acts in an analogous fashion as a repulsive guidance factor for these developing trunk vessels via a novel endothelial-specific plexin receptor. Our results thus highlight similarities between the establishment of anatomical pattern in the developing vascular and nervous systems. ■

Poolesville Digs

The 500-acre NIH Animal Center in Poolesville, Md., offers housing and research services for a variety of animals, including primates, ungulates, poultry and waterfowl, and rodents. Housing options include conventional, sun-protected, barrier, and hazard-containment environments. For more information on services and capabilities at the Poolesville site, call the Division of Veterinary Resources at 301-496-2527. ■

Catalytic Reactions?

If you have a photo or other graphic that reflects an aspect of life at NIH (including laboratory life) or a quotation that scientists might appreciate that would be fit to print in the space to the right, why not **send it to us via e-mail: catalyst@nih.gov>; fax:402-4303; or mail: Building 2, Room 2E26.**

Also, we welcome "letters to the editor" for publication and your reactions to anything on the *Catalyst* pages.

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- Rotavirus Vaccine Again a Reality
- NIH Tech Transfer
- People & Programs In the IRP: A Series

Kids' Catalyst

Striped Ice

It's cold out there! While you're enjoying your winter, try this experiment to produce some Striped Ice. What you'll need is:

1. Water
2. Minute timer
3. Two drinking glasses (made of glass, to see the effect better)
4. Patience
5. Liquid food coloring; you'll need at least one color, but a great combination is red and blue.
6. Experiment sheet with the headings "Time" and "Color"

Now take your glasses and fill them with water. Using the food coloring, make the water in one glass red, and the water in the other blue—make sure the color is dark.

Put both glasses in the freezer, set your timer for an hour, and go play in the snow (or do some homework). You should see ice forming on the top and sides of the glass, usually in some extraordinary patterns. Wait until enough ice has formed that there's a solid coat of ice on the inside of the glasses.

Chip away at the surface of the ice so you can pour out the water from each color into other, empty glasses. This extra water can be used right away—by pouring red water into the blue-ice glass, and vice versa. Check the time, and come back in another hour. Now you have an alternate stripe!

Experiment with timing, different size and shape of glasses, slanted striping, and colors. (Remember, of course, to write down all of your findings.) Don't worry if you forget to come back in an hour—water freezes from the outside surface in.

Wonder how it melts, and what color it will turn into when it melts?

Keep warm, and no matter how much ice you have outside, you can make some really nice ice inside!

—Jennifer White

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